The Chemistry on Diterpenoids in 1965

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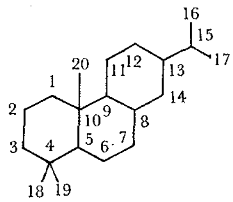
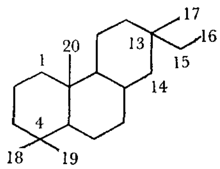
I. INTRODUCTION

Several reviews on diterpenoids have been published.*2 Last year, the author described the chemistry on diterpenoids in 1964 in outline.[1] The present review is concerned with the chemical works on diterpenoids in 1965.

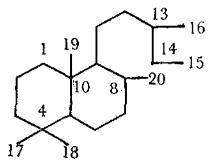
The classification consists of abietanes, pimaranes, labdanes, phyllocladanes, gibbanes, diterpene alkaloids, and the others.



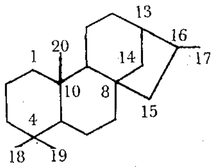
Abietane



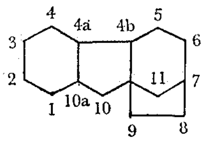
Pimarane



Labdane



Phyllocladane



Gibbane

II. ABIETANE AND ITS REOATED SKELETONS

Lawrence *et al.*[2] isolated palustric acid (**2**) from gum rosin. The selective crystallization of its 2,6-dimethylpiperidine salt, which precipitated from acetone solution of the rosin, from methanolacetone (1:1) was effective for isolation.

The four conjugated dienic resin acids, namely, levopimaric (**1**), palustric (**2**), neoabietic (**3**), and abietic acid (**4**) were treated with an excess of potassium *t*-butoxide in dimethyl slufoxide solution at reflux temperature (189°) for 2 minutes.[3] All four solutions then exhibited a single major peak in their U.V. spectra characteristic of abietic acid. The acids were allowed to react with diazomethane and the reaction mixtures were analyzed by g.l.c. The major result of the base-catalyzed

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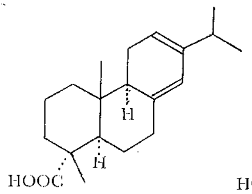
*2 See references cited in the review[1] published last year by the author.

reaction was the isomerization of the resin acids to abietic acid, similar to their behavior in acid solution.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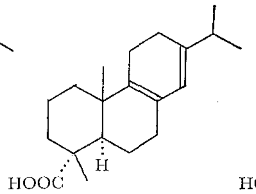
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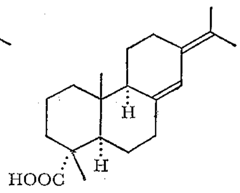
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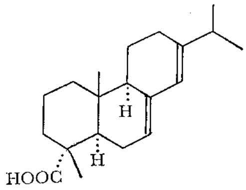
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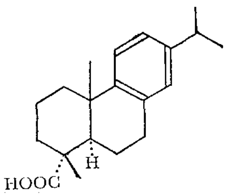
The N.M.R. spectra of the derivatives of dehydroabietic (**5**) and podocarpic acid (**6**) and of their 5-epimers were discussed by Wenkert *et al.*[4] A correlation of the chemical shifts of methyl groups and other side chains was presented. The stereochemistry of the conformationally flexible A/B *cis* compounds was analyzed.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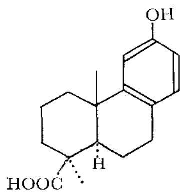
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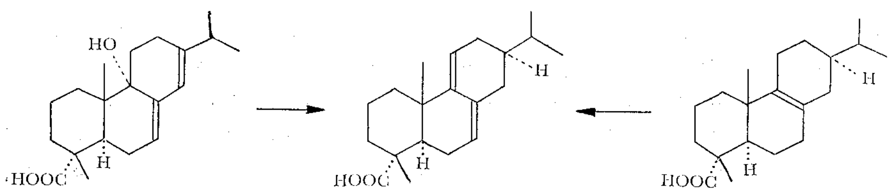
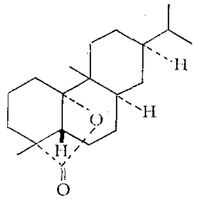
Oxidation of abietic acid (**4**) with selenium dioxide furnished dehydroabietic acid (**5**) and a hydroxyabietic acid which had been assigned formula 12-hydroxyabietic acid by Fieser and Campbell.[5] The structure of the latter was revised to 9-hydroxyabietic acid (**7**) by Herz and Wahlborg.[6] The assignment was based on spectroscopic evidence and its conversion to $\Delta^{7,9(11)}$-abietadienoic acid (**8**) which was in turn synthesized from $\Delta^{8(9)}$-abietenoic acid (**9**). In the course of this work, an


(7) (8) (9)

entry into the pseudoabietic acid series has been effected and the stereochemistry of the various lactones, e.g. **10**, **11**, and **12**, belonging to this series has been elucidated. The γ-lactone **11** is unstable and is quickly isomerized to δ-lactone **12** which then yields an equilibrium mixture of **10** and **12**.



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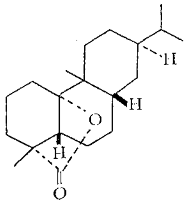

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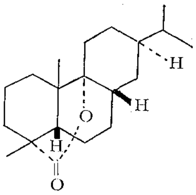
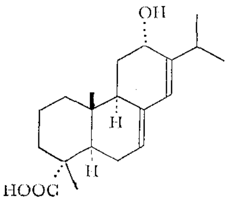


(12)

Herz *et al.*[7] treated levopimaric acid (**1**) with hypochlorous acid in a basic solution to give 12α-hydroxyabietic acid (**13**). The latter was established by an independent synthesis from levopimaric acid peroxide. Hydrogenation gave two dihydro derivatives, **14** and **15**, and a tetrahydro derivative **16**. The O.R.D. curves of 12-keto 8α-H-abietanes were discussed.



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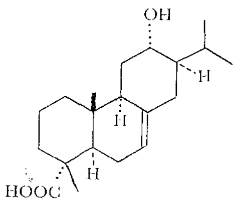

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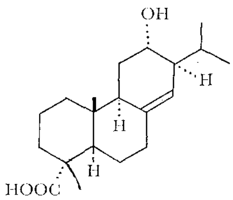

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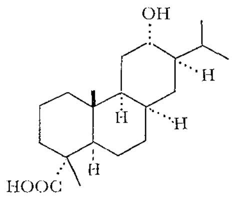
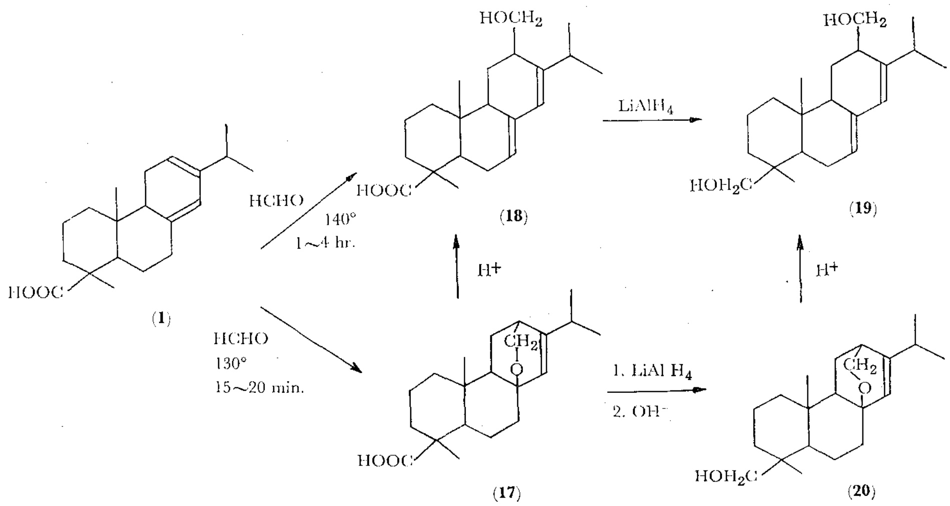
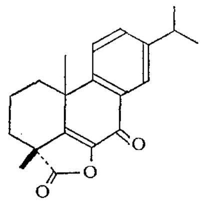


(16)

The Diels-Alder reaction of levopimaric acid (**1**) with formaldehyde yielded adduct **17** in high yield.[8] The cleavage of the ether linkage of compound **17** was effected in acidic condition to give 12-hydroxymethylabietic acid (**18**). The latter on reduction with lithium aluminum hydride gave diol **19**, which was in turn derived from adduct **17** *via* **20** by reduction and treatment with acid.



Wenkert and Mylari[9] carried out a reduction of the enol lactone **21** with sodium borohydride and got a new hydroxylactone **22**. Jones oxidation of this compound yielded a new ketolactone **23** whose sodium borohydride reduction reyielded the hydroxylactone while calcium-ammonia reduction, followed by hydrogenation, gave 5-isodehydroabietic acid (**24**).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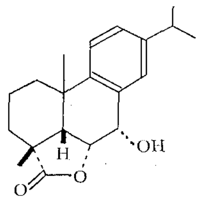
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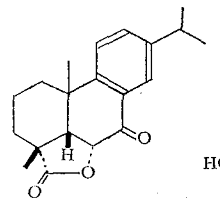
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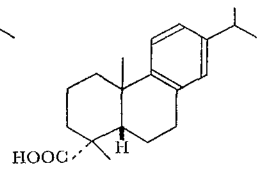
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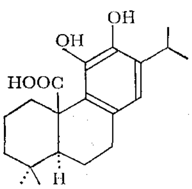
On the basis of the N.M.R. analysis, Narayanan and Linde[10] proposed the A/B *trans* stereochemistry **25** for salvin (=carnosic acid), whose plain structure had been proposed by Linde.[11] They also proposed the structure of picrosalvin (=carnosol) including the absolute configuration as formula **26**; the conversion of salvin to picrosalvin had been carried out. These suggestions are completely identical with the conclusions published already by Wenkert *et al.*[12]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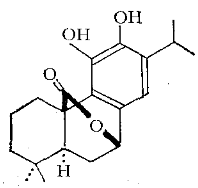
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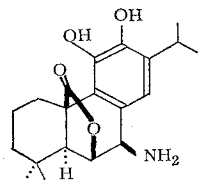
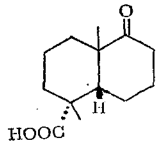

(27)

Russian workers[13] had reported the presence of an alkaloid, rosmaricine, in *Rosmarinus officinalis*. Wenkert *et al.*[14] isolated rosmaricine from the leaves of the plant according to the method of Russian workers, and determined its structure as formula **27**. However, when rosemary leaves were extracted without the use of ammonia, no rosmaricine or other basic substances could be detected among the plant constituents. Contrastingly, exposure of the same plant extracts to ammonia and air led to the production of rosmaricine. Exposure of the extracts to sodium carbonate solution yielded no rosmaricine. A further detailed investigation resulted in a suggestion that rosmaricine (**27**) and carnosol (=picrosalvin) (**26**) must be artifacts from carnosic acid (=salvin) (**25**).

Dutta *et al.*[15] synthesized bicyclic ketoacid **28**, the stereochemistry of which was established by its conversion to methyl 5-epideisopropyldehydroabietate (**29**). They also recognized that the heating of compound **30** with palladium on charcoal gave methyl deisopropyldehydroabietate (**31**) in poor yield. They reached a complete agreement with Spencer's conclusion.[16]



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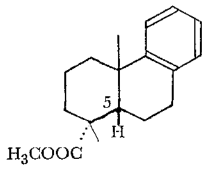

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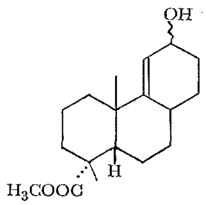

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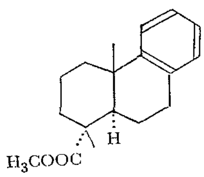
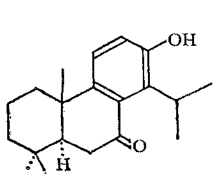


(31)

Cambie *et al.*[17] investigated O.R.D. and C.D. curves of α-bromo derivatives of cyclohexanones conjugated to an aromatic ring; the α-bromo derivatives of 7-oxo-totarol (**32**), sugiol (**33**), 7-oxo-podocarpic acid (**34**), and 7-oxo-dehydroabietic acid (**35**) were studied.



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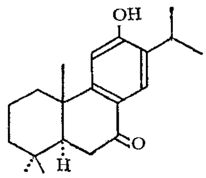

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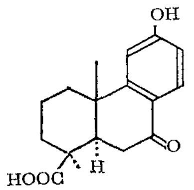

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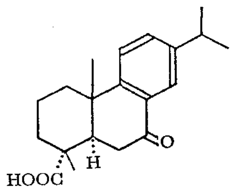
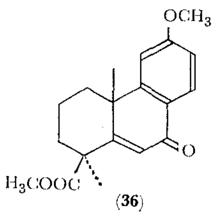


(35)

In a study of synthesis of the parent chromophore in a triterpenoid, pristimerin, Hill *et al.*[18] attempted the reduction of methyl 0-methyl-$\Delta^{5(6)}$-7-oxo-podocarpate (**36**) to deoxo compound **37**, but they could not get a good result.



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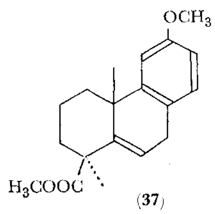
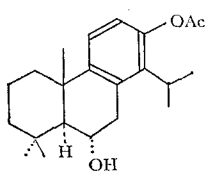


(37)

Dehydroabietylamine was advantageously used to separate (+)-enantiomorph of racemic α-phenoxypropionic acid and D-(−)-enantiomorph of racemic α-benzyloxycarbonylaminophenylacetic acid.[19]

Taylor *et al.*[20] investigated a lead tertaacetate oxidation of 14-isopropylpodocarpa-8,11,13-triene-6α,13-diol 13-monoacetate (**38**); they got a cyclic ether **39**, in which the ring A has a boat form.



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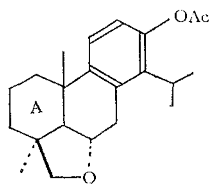

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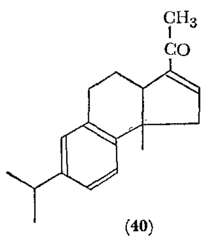

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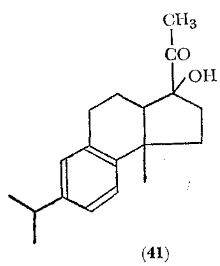
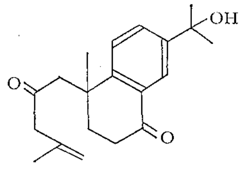


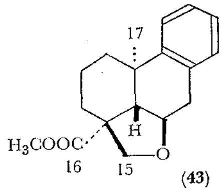
(41)

Huffman and Arapakos[21] synthesized tricyclic steroid analogs **40** and **41** from dehydroabietic acid (**5**), and gave a discussion on their stereochemistry.

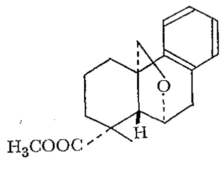
Grelach[22] isolated Solidago-diterpene A from the root of *Solidago canadensis* and *S. gigantea*, and assigned structural formula **42** on the basis of spectral and chemical evidences.



(**42**)



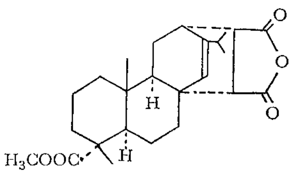
(**43**)



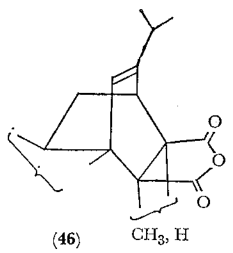
(**44**)

Tahara *et al.*[23] derived methyl 6β,15-epoxy-enantiopodocarpa-8,11,13-trien-10-oate (**43**), methyl 6α,17-epoxyenantiopodocarpa-8,11,13-trien-16-oate (**44**), and their derivatives from abietic acid (**4**). These compounds are useful as potential intermediates for the syntheses of the other natural diterpenoids.

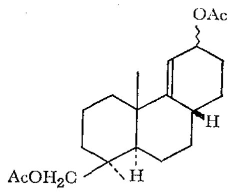
The reactions between *p*-nitroperbenzoic acid and certain Diels-Alder addition compounds in the diterpene series, e.g. **45** and **46**, were investigated.[24] Cis opening of an epoxy group was also observed.



(**45**)

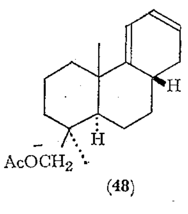


(**46**)

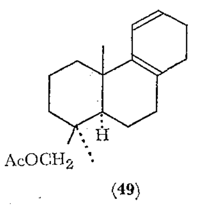


(**47**)

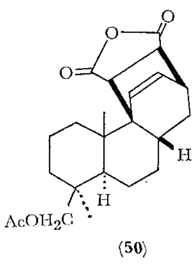
Girotra and Zalkow[25] got a mixture of dienes **48** and **49** from pyrolysis of diacetate **47** which was derived from podocarpic acid (**6**). Subsequent Diels-Alder reaction with maleic anhydride yielded two kinds of crystalline adducts **50** and **51**.



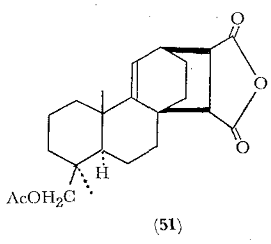
(**48**)



(**49**)

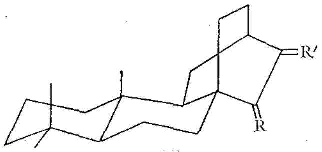


(**50**)

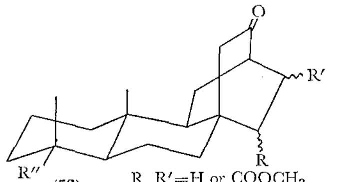


(**51**)

Zalkow *et al.*[26] examined the O.R.D. of such types of compounds as **52** and **53**.

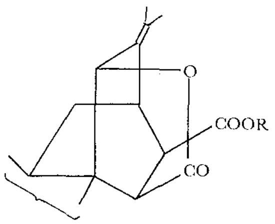


(52) ($R=H_2$, $R'=O$) and ($R=O$, $R'=H_2$)

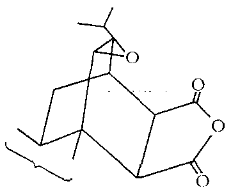


(53) R, $R'=H$ or $COOCH_3$
$R''=CH_3$ or $COOCH_3$

They[27] also carried out ozonolysis of methyl maleopimarate (**45**), obtaining compounds **55** and **56** in addition to the known product **54**.[28] The revised formulas given by them to the former two compounds were not in agreement with those proposed by Ruzicka *et al.*[29][30]



(54)



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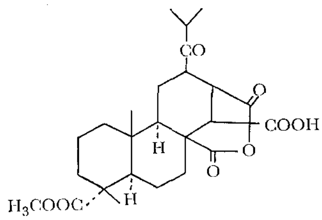
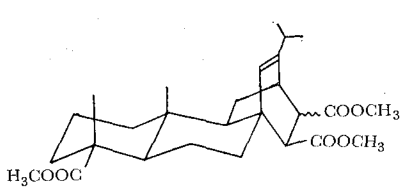


(56)

Attempted epoxidation[27] by trifluoroperacetic acid of trimethyl maleopimarate (**57**, ~~~$COOCH_3$: β) and isomeric trimethyl fumaropimarate (**57**, ~~~$COOCH_3$: α) gave a hydroxy lactone **58** and epoxy triester **59**, respectively.



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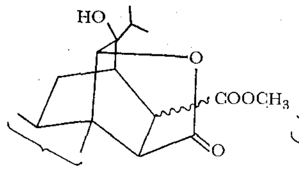

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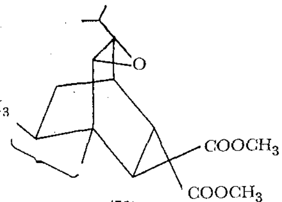
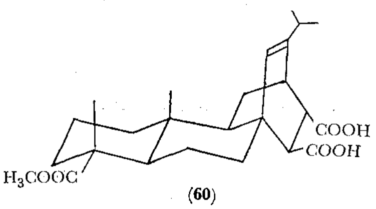


(59)

Ayer and McDonald[31] got acid **61**, diene **62**, and two kinds of lactones **63** and **64** by a lead tetraacetate oxidation of methyl fumaropimarate (**60**). They also described a speculation on their mode of formation.



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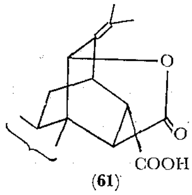

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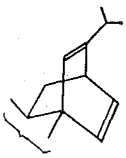

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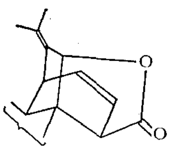

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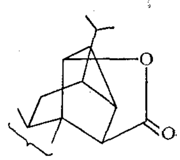
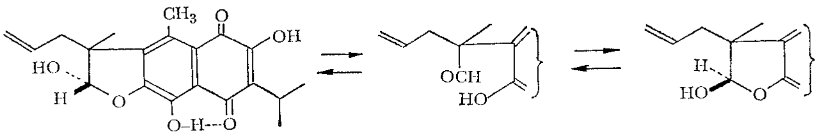


(64)

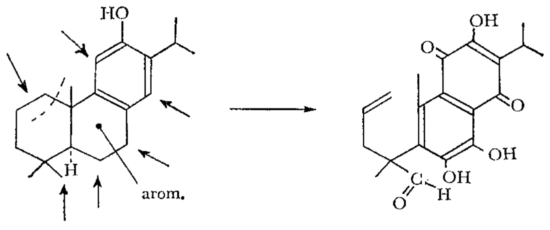
Karanatsios and Eugster[32] investigated the structure of coleone A, one of the leaves pigments from *Coleus igniarius* (Labiatae), and assigned the structural formula

65 to the substance on the basis of the results of various chemical reactions and spectroscopic data.



(65)

They considered the biogenesis of coleone A as shown in Scheme 1, and seeked for a phenolic precursor in the same plant source. But, they could not isolate any phenolic substance.



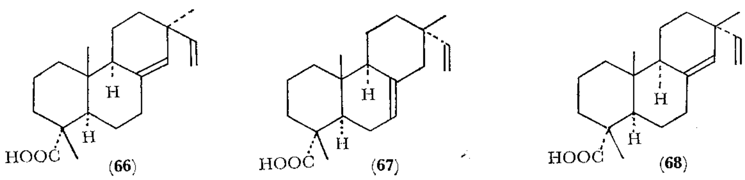
Ferruginol

Coleone A

Scheme 1

III. PIMARANE AND ITS RELATED SKELETONS*

Edwards *et al.*[33] provided an evidence on the epimeric character of C-13 substituents of pimaric acid (**66**) and isopimaric acid (**67**). They also gave an evidence of nuclear double bond location in isopimaric acid. Thus, the structure and stereochemistry of isopimaric acid were determined as **67**.



(66) (67) (68)

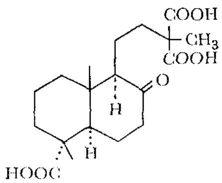
Wenkert *et al.*[4] discussed on N.M.R. spectra of pimaric acid (**66**), isopimaric acid (**67**), and sandaracopimaric acid (**68**).

ApSimon *et al.*[34] proved that tetrahydro derivatives of pimaric acid (**66**), isopimaric acid (**67**), and sandaracopimaric acid (**68**) have *trans-anti-trans* fused skeletons, and discussed the implications of this observation.

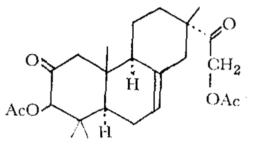
Both of isopimaric acid (**67**) and pimaric acid (**66**) on ozonolysis give a same ketocarboxylic acid **69**. Enzell and Thomas[35] investigated ozonolysis and perphthalic acid oxidation on compounds having a double bond between C-7 and C-8,

* See also ref. 85 (Section V).

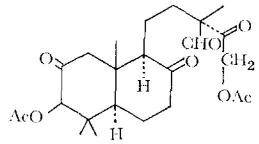
and observed the similar anomalous ozonolyses; araucarolone diacetate (**70**) on ozonolysis followed by reduction with zinc and acetic acid gave as main product an epoxide (65%) together with a samll yield of the ketoaldehyde **71** (20%). To



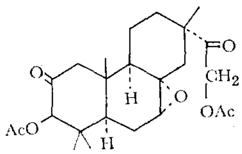
(**69**)



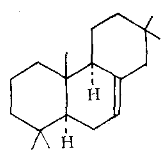
(**70**)



(**71**)



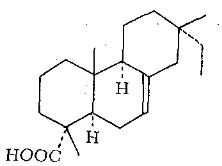
(**72**)



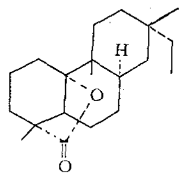
(**73**)

demonstrate the structure of the epoxide, araucarolone diacetate was treated with monoperphthalic acid in ether. The product was a mixture of four epoxides, one of which was identical with the ozonolysis epoxide. Structural formula **72** was assigned to this epoxide on the basis of analysis, infrared spectrum, and N.M.R. data. They studied also the action of ozone and of monoperphthalic acid on the simpler analog, 16-norpimar-7-ene (**73**). From the results obtained, they discussed on the reaction route for this anomalous ozonolysis.

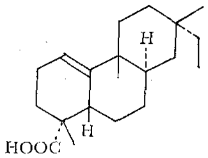
Herz and Mirrington[36] synthesized (–)-rimuane (**79**) from isopimaric acid (**67**); lactonization of dihydro derivative **74** of the starting material by the method of Edwards and Howe[37] to compound **75** and hydrolysis of the latter with potassium hydroxide in refluxing diethylene glycol afforded acid **76**. Subsequent lithium aluminum hydride reduction and catalytic hydrogenation under the addition of a



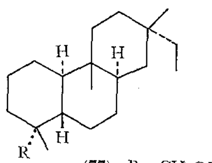
(**74**)



(**75**)



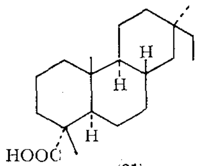
(**76**)



(**77**): R=CH_2OH
(**78**): R=CHO
(**79**): R=CH_3

trace of perchloric acid gave saturated alcohol **77**. Oxidation of **77** with Jones reagent at 0° yielded aldehyde **78** which afforded (–)-rimuane (**79**) when subjected to Huang-Minlon reduction.

The same authors[38] investigated the stereochemistry of the tetrahydropimaric acids. Hydrogenation of dihydropimaric acid (**80**) at 20° and at atmospheric pressure gave a tetrahydropimaric acid, which had been given the suggestion that this might be *trans-anti-trans* isomer **81** by a French group.[39] The suggestion was now clarified to be correct by an unambiguous synthesis by the American group.



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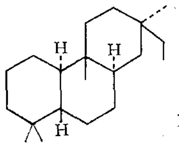

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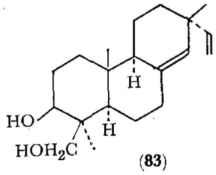

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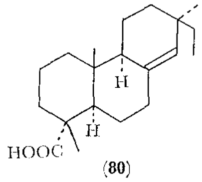
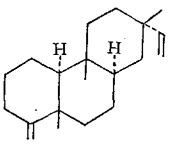


(80)

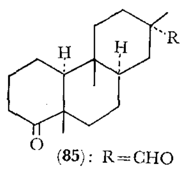
Herz and Mirrington[40] also carried out the conversion of pimaric acid (**66**) to (–)-13-*epi*-rimuane (**82**). The route is similar to that in which (–)-rimuane (**79**) was derived from isopimaric acid (**67**). (See above.)

Grant and Munro[41] elucidated, on the basis of the several chemical evidences and N.M.R. data, the structure of compound B, a diterpene diol from heartwood extractives of *Dacrydium colensoi* to be sandaracopimaradiene-3β,19-diol (**83**).

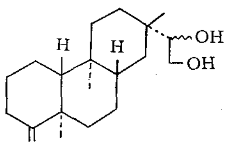
Connolly, Kitahara *et al.*[42] showed that keto-aldehyde **85**, the ozonolysis product of dolabradiene (**84**), is different from keto-aldehyde **87** derived from erythroxydiol Y (**86**), and that monoketones **88** and **89**, partial reduction products of keto-aldehydes, are enantiomeric each other. Thus, a further evidence on the same configuration of C–13 in dorabradiene (**84**) and erythroxydiol (**86**) was presented.



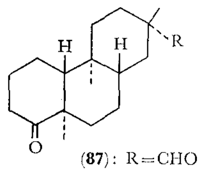
(84)



(85): R=CHO
(88): R=CH_3

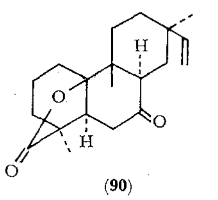


(86)

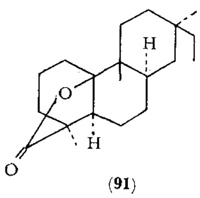


(87): R=CHO
(89): R=CH_3

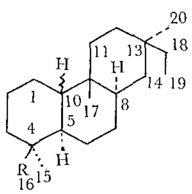
Whalley *et al.*[43] gave an active demonstration for the location of the carboxy group in rosenonolactone (**90**), a diterpenoid metabolite from *Trichothecium roseum*; reduction by the Clemmensen process of 10-hydroxy-rosan-16-oic γ-lactone (**91**) gave rosan-16-oic acid (**92**), which was converted by way of the ester **93** into rosan-16-ol (**94**). Dehydrogenation of the alcohol with phosphorus pentachloride gave a



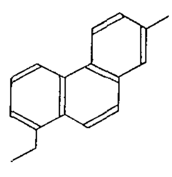
(90)



(91)



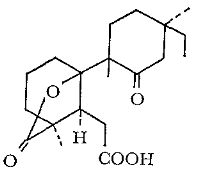
(92): R=COOH
(93): R=$COOCH_3$
(94): R=CH_2OH



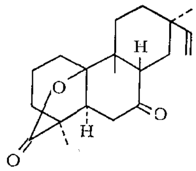
(95)

halogenated hydrocarbon which, after successive treatment with boiling quinoline and then sodium, was dehydrogenated to yield 1-ethyl-7-methylphenanthrene (**95**).

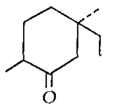
Further examination of rosic acid (**96**), together with an investigation of the isomeric



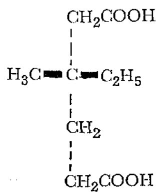
(**96**)



(**97**)



(**98**)



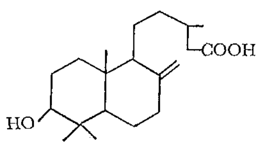
(**99**)

triols obtained by reduction of dihydrorosenono- and dihydroisorosenono-lactone, substantiated the structure **90** of the metabolite and enabled the relative stereochemistry of rosenono- (**90**) and isorosenono-lactone (**97**) to be defined.

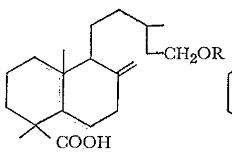
The absolute configuration of C–13 in rosenono- and rosolo-lactone was also established by Whalley *et al.*[44]; degradation of (+)-5-ethyl-2,5-dimethylcyclohexanone (**98**) derived from ring C of dihydrorosenonolactone gave (+)-3-ethyl-3-methyladipic acid (**99**).

IV. LABDANE AND ITS RELATED SKELETONS*

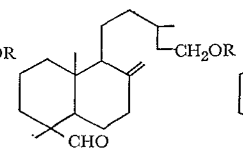
Weissmann and Bruns[45] isolated a hydroxyditerpenecarboxylic acid from the resin of *Araucaria imbricata* (*A. araucana*) and reported its identity with acid **100** which was isolated by Chandra *et al.*[46] from *A. imbricata.* But later, the same authors[47] by themselves denied the aforegoing identity and reported the isolation of acetoxy acid **101**, hydroxy acid **102**, acetoxy aldehyde **103**, hydroxy aldehyde **104**, and diol **105**.



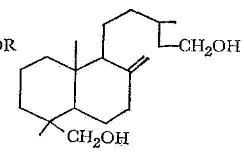
(**100**)



(**101**): R=Ac
(**102**): R=H

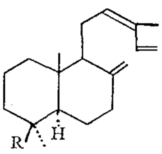


(**103**): R=Ac
(**104**): R=H

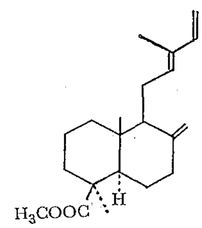


(**105**)

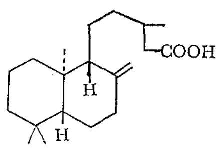
Lawrence *et al.*[48] showed the identity of elliotinoic acid, which is isolated from the oleoresin of the slash pine (*Pinus elliottii*), with communic acid (**106**), and also the identity of elliotinol isolated from the same plant source with compound **107**, which up to that time had not been observed in nature, but had been obtained only as a reduction product of methyl communate.



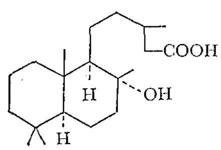
(**106**): R=COOH
(**107**): R=CH_2OH



(**108**)



(**109**)



(**110**)

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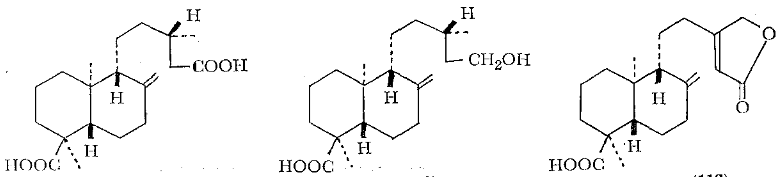
* See also ref. 143 (Section VIII).

Norin[49] compared N.M.R. and U.V. spectra of methyl communate with those of *trans*-ocimenes and recognized their similarity. Thus, he assigned the *trans* configuration to the side chain as shown in formula **108**.

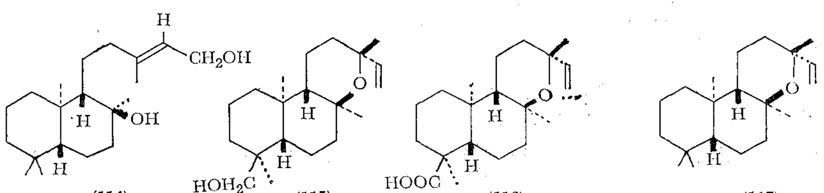
Graham and Overton[50] proved that eperuic acid* and labdanolic acid* are antipodal apart from C–8 and C–13, as shown in formulas **109** (eperuic acid) and **110** (labdanolic acid). The *trans-syn*-configuration previously assigned to eperuic acid can therefore be discounted and with it the last apparent exception among diterpenoids to the rule of A/B/C *trans-anti*-stereochemistry.

Henrick and Jefferies[51] isolated new diterpene acids, eperu-8(20)-ene-15, 18-dioic acid (**111**), 15-hydroxyeperu-8(20)-en-18-oic acid (**112**) and the $\Delta^{\alpha\beta}$-butenolide **113** from *Ricinocarpus muricatus*.



(**111**) (**112**) (**113**)

Jefferies and Payne[52] isolated four new diterpenes and six known diterpenes from a new *Beyeria* species. Three of the new diterpenes were labdane derivatives **114**, **115**, and **116**, and another one was kaurane derivative (see Phyllocladane section). One of the known diterpenes was 13-*epi*-(–)-manoyl oxide (**117**).

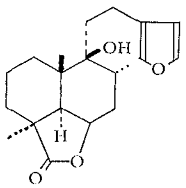


(**114**) (**115**) (**116**) (**117**)

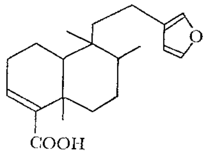
The stereochemistry of marrubiin, a major crystalline constituent of *Marrubium vulgare*, was shown to be **118** by Fulke and McCrindle[53] on the basis of N.M.R. data, provided that a residual uncertainty on the stereochemistry of C–9 remains. Breccia *et al.*[54] investigated the incorporation of [1,4-^{14}C]-succinic acid and [2.,3-^{3}H]-succinic acid into *Marrubium vulgare*, and suggested that at least three carbon atoms of each succinic acid unit are involved in the marrubiin biogenesis, and the pathway of incorporation of [1,4-^{14}C]-succinic acid into marrubiin *via* isoprenic units could involve only one -^{14}COOH of the acid for each isoprenic unit.

Cocker *et al.*[55] isolated from ligroin extract of *Copaifera officinalis* a dextrorotatory hardwickiic acid (**119**), an enantiomer of the acid isolated by Dev *et al.*[56] from *Hardwickia pinnata*.

* See below; ref. 63.



(118)



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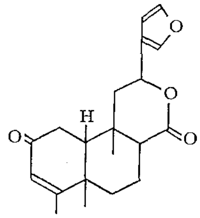
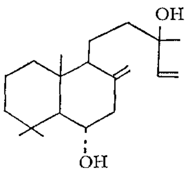


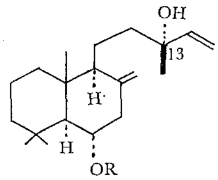
(120)

Tinophyllone, a diterpenoid from *Tinomiscium philippinense,* was shown to have structure **120** by G. Aguilar-Santos.[57]

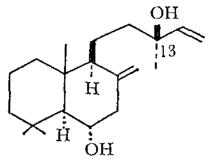
The chemistry of larixol, a constituent from *Larix* resin, was investigated by three groups. Haeuser[58] assigned structure **121** to larixol which was obtained from larch resin by alkaline hydrolysis of the neutral fraction extracted by petroleum ether. Norin *et al.*[59] investigated the structures and configurations of larixol and larixyl acetate, and proposed formulas **122** and **123**. Sandermann and Bruns[60] studied the chemistry of larixol. They also studied on its configuration and assigned the stereochemistry **124**.[61]



(121)



(122) : R=H
(123) : R=Ac



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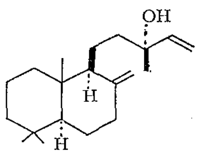

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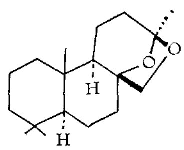
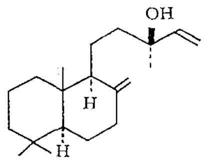


(126)

The configuration of C–13 is only a different point between **122** and **124**. Norin *et al.*[59] converted larixol into 13-*epi*-manool (**125**) *via* tosylation followed by lithium aluminum hydride reduction. On the basis of this conversion, they determined the stereochemistry of C–13. On the other hand, Sandermann and Bruns[61] compared oxidation products from larixol and manool. On treatment with potassium permanganate in acetone and dehydroxylation, larixol gave a ketal **126**, which was identified with the sample obtained from manool (**127**) by Schenk *et al.*[62] Moreover, ketol **128** on Wolff-Kishner reduction gave tetrahydromanool (**129**). From these results, they concluded the stereochemistry of C–13 to be shown in **124**.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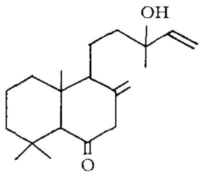
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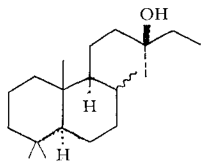
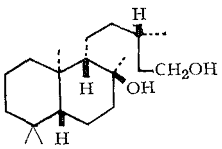

(129)

Henrick and Jefferies[63] isolated three new diterpenes from *Ricinocarpus muricatus* and showed their structures to be eperuane-8β,15-diol (**130**), eperuane-8β,15,18-triol (**131**), and 15, 16-dihydroxyeperu-8(20)-en-18-oic acid (**132**). They also showed that eperuic acid* (**133**) and labd-8(20)-en-15-oic acid are antipodal apart from C–13.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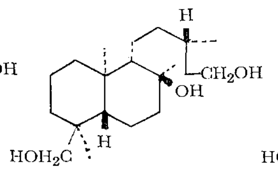
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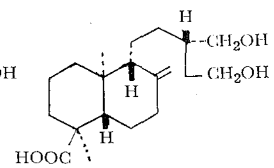
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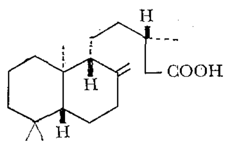
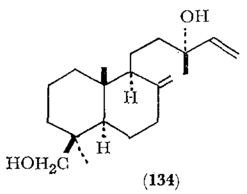

(133)

Rowe and Shaffer[64] revised structures[65] posturated for diterpenes isolated from *Pinus contorta*; "hydroxy*epi*manool" is 13-*epi*torulosol (**134**), "contortadiol" is identical with agathadiol (**135**), and "contortolal" should be renamed agatholal (**136**).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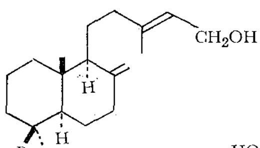
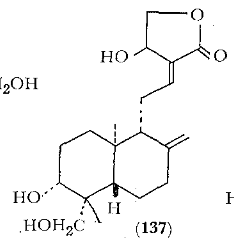

(135): R=CH_2OH
(136): R=CHO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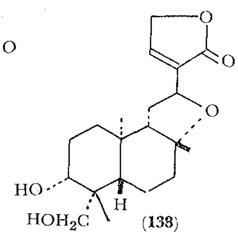
(138)

Cava *et al.*[66] prepared a number of new transformation products of andrographolide (**137**). The structure of iso-andrographolide, an acid transformation product of andrographolide, was shown to be **138**. The stereochemistry of C–3 and C–9 in andrographolide was proved to be shown in **137** from chemical results. The configuration of C–4 substituents was supported by N.M.R. data.

Grant *et al.*[67] isolated three oxido-diterpenes from *Dacrydium colensoi* and characterized them to be 2α-hydroxymanoyl oxide (**139**), 2,3-dicarboxy-2,3-secomanoyl oxide (**140**), and 2-oxo-3-oxamanoyl oxide (**141**). Grant and Munro[68] showed the structure of another oxidoditerpene isolated from the heartwood of *D. colensoi* to be 18-hydroxy-2-ketomanoyl oxide (**142**).

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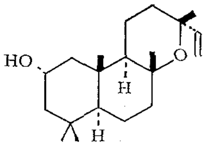
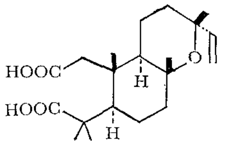
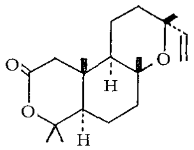
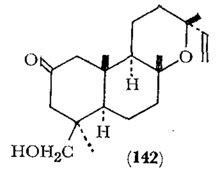
* See above; ref. 50 and structural formula 109.

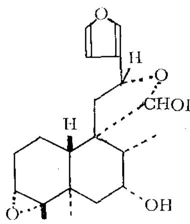

(139)


(140)


(141)


(142)

Halsall *et al.*[69] showed the structure of cascarillin A, an epoxy-furanoid diterpene isolated from *Cascarilla* bark to be **143**. Mousseron-Canet and Mani[70] studied selective epoxidations of manool, manoyl acetate, and manoyl formate. Bory and Fetizon[71] synthesized manoyl oxide (**144**) by Hofmann degradation of quaternary base **145**. Sibirtseva *et al.*[72] investigated the structure of the carbonyl compound formed in oxidation of sclareol (**146**) with chromate mixture and showed it to be **147**. Kucherov *et al.*[73] tried the acid-catalyzed cyclization of monocyclofarnesyl-acetone and found a new route of stereospecific cyclisation of isoprenoids.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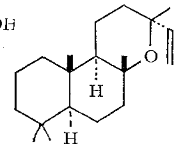
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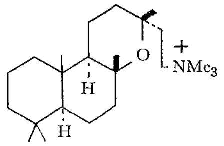
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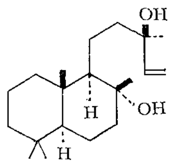
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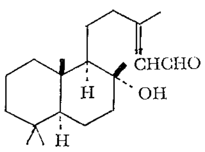
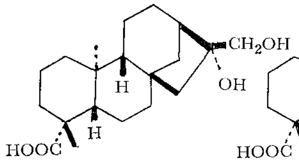

(147)

V. PHYLLOCLADANE AND ITS RELATED SKELETONS

Jefferies and Payne[52] isolated many kinds of diterpenes from a new *Beyeria* species. One of the new diterpenoids belongs to kaurane derivative. The structure was shown to be **148**. The known substances of this group which were isolated from the same plant source were (—)-kaur-16-en-19-oic acid (**149**), 16β-(—)-kaurane-16, 17, 19-triol (**150**), and 16α-(—)-kaurane-3α, 17, 19-triol (**151**). Moreover, diol **152** and hydroxy acid **153**, both of which had not yet been isolated from natural source, but had been already derived from diacid **154**, were isolated.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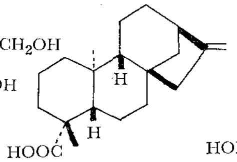
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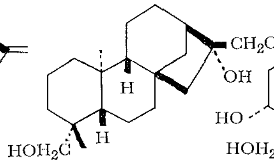
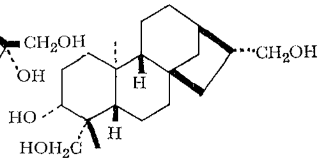
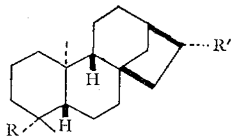
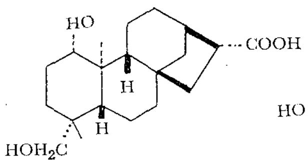

(150)


(151)

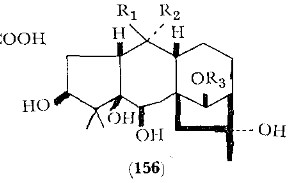
Henrick and Jefferies[74] isolated the known 16, 17-dihydroxy-16β-(—)-kauran-19-oic acid (**148**) and a new acid, that is, 1α, 19-dihydroxy-16α-(—)-kauran-17-oic acid (**155**) from *Ricinocarpus stylosus*. The latter is a first example of 1α-hydroxy-(—)-kaurane derivative, and an interesting compound as a possible precursor of enmein (**282**) and grayanotoxin (**156**) in the biogenesis.



(152): R=R'=CH_2OH
(153): R=COOH R'=CH_2OH
(154): R=R'=COOH

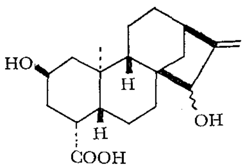


(155)



(156)

Quilico *et al.*[75] investigated the structure of atractyligenin, the aglycone of atractyloside and proposed structure **157** to it.



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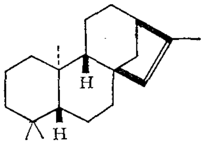
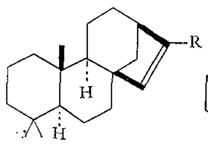
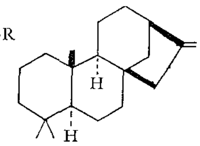


(158)

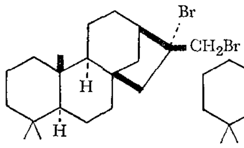


(159): R=CH_3
(160): R=H



(161)

Briggs *et al.*[76] studied the reaction of N-bromosuccinimide on (—)-isokaurene (**158**), isophyllocladene (**159**), and 17-norphylloclad-15-ene (**160**). Phyllocladene (**161**) on bromination with bromine in carbontetrachloride gave dibromo derivative **162**, which was dehydrobrominated during the chromatography on alumina to yield 17-bromophylloclad-15-ene (**163**). The latter was identical with the N-bromosuccinimide bromination product of isophyllocladene (**159**).



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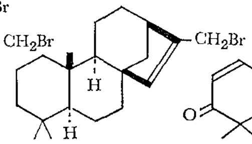

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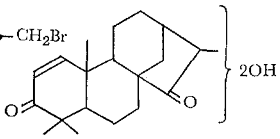

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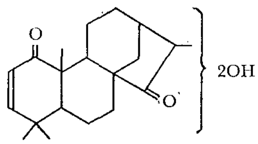
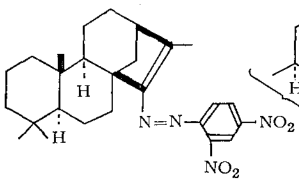


(165)

Elizarava and Kuzoukov[77] suggested partial structure **164** or **165** to plectrin, a diterpene.

Briggs *et al.*[78] revised the structures **166** and **167** postulated previously for the products of the reaction between isophyllocladene (**159**) and diazotised 2, 4-dinitroaniline to **168** and **169**, respectively.



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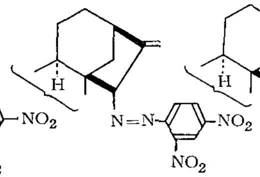

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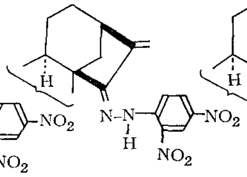

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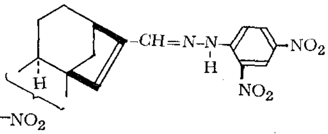
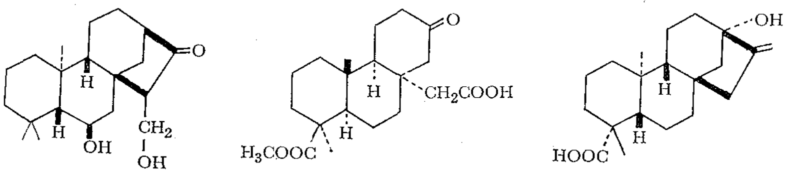


(169)

Jiménez *et al.*[79] studied the stereochemistry of a degradation product from tubicorytin and presented its steric structure **170**; the stereochemistry of tubicorytin was elucidated except that at C-16.

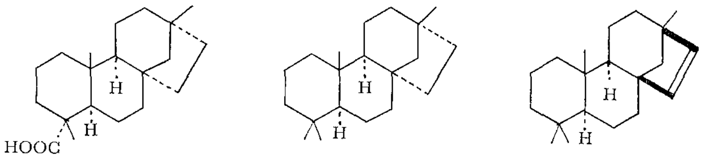


(170) (171) (172)

Mori and Matsui[80] synthesized methyl (±)-8α-carboxymethyl-podocarpan-13-one-4β-carboxylate (as **171**), a degradation product of steviol (**172**).

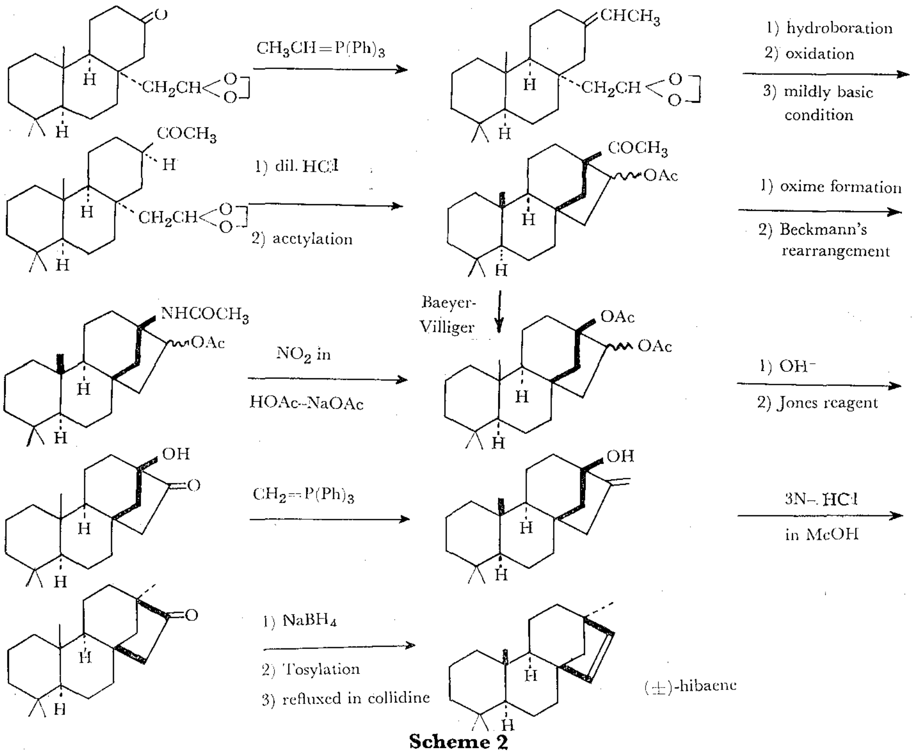
Herz *et al.*[81] synthesized dihydroisohibaic acid (**173**) and isohibane (**174**) from isopimaric acid (**67**).

Kitahara and Yoshikoshi[82] published a detailed paper on the structure and stereochemistry elucidation of hibaene (**175**), a diterpene from the leaves of *Thujopsis dolabrata.*



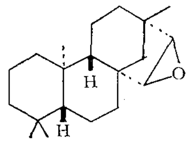
(173) (174) (175)

Ireland and Mander[83] carried out the total synthesis of (±)-hibaene. The route is shown in Scheme 2 (Each compound represents *d,l*-compound.).

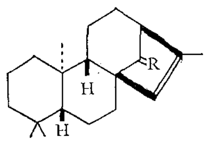


Scheme 2

Kapadi and Dev[84] converted (+)-hibaene (antipode of **175**) into (−)-kaurene. They carried out BF_3-catalyzed rearrangement of epoxide **176** to unsaturated alcohol **177**, which was oxidised to ketone **178** and then converted to kaurene (**179**) by Wolff-Kishner's reduction. Dev *et al.*[85] isolated (+)-hibaene, (−)-pimaradiene, and three new diterpenes from *Erythroxylon monogynum*. They assigned structures **180**, **181**, and **182** to (−)-atisirene, (−)-isoatisirene, and (+)-devadarene, respectively.

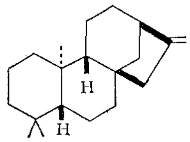


(**176**)

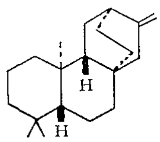


(**177**): R=<$^{OH}_{H}$

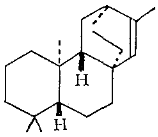
(**178**): R=O



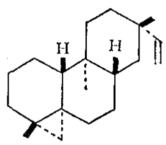
(**179**)



(**180**)



(**181**)

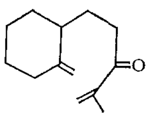


(**182**)

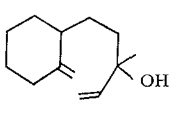
VI. GIBBANE AND ITS RELATED SKELETONS

Borchert[86] examined rejuvenation of apical meristens in *Acasia melanoxylon* by gibberellic acid. Maheshwari and Johri[87] found gibberellin-like active substances during seed development in *Zephyranthes lancasteri*.

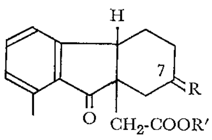
Dolby and Iwamoto[88] examined the acid-catalyzed cyclizations of dienone **183** and allylic alcohol **184** as models for the synthesis of the C-D ring system of gibberellic acid and related compounds. Neither compound gave rise to the desired tricyclic materials in appreciable yield. The preparation of allylic alcohol **184** and dienone **183** were described.



(**183**)



(**184**)



(**185**): R=O, R′=H

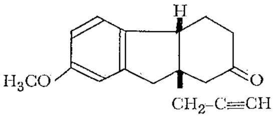
(**186**): R=C_7 <$^{O}_{O}$], R′=H

(**187**): R=C_7 <$^{O}_{O}$], R′=CH_3

(**188**): R=C_7 <$^{O}_{O}$], R′=$C(CH_3)_3$

House and Darms[89] reported an improved synthetic route of hexahydrofluorene derivative **185**. They prepared its monoethylene ketal carboxylic acid **186** and esters **187** and **188**. The sodium borohydride reduction of the latter two esters gave diols.

Stork *et al.*[90] carried out a cyclization of compound **189** with potassium in a mixture of tetrahydrofuran and anhydrous ammonia containing ammonium sulfate and separated tetracyclic alcohol **190** from the reaction mixture. The alcohol was converted to ketone **191** by acid-catalyzed rearrangement.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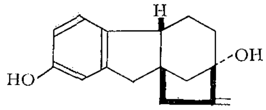
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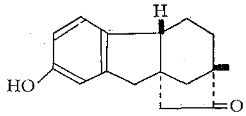
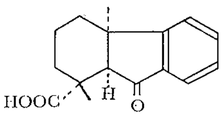

(191)

Banerjee *et al.*[91] published a stereoselective total synthesis of (±)-hexahydrofluorenone carboxylic acid **192** (represented as an enantiomer). The cyclization of B-ring consisted of the heating of ester **193** with polyphosphoric acid.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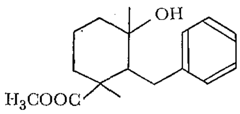
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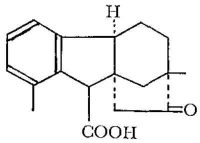
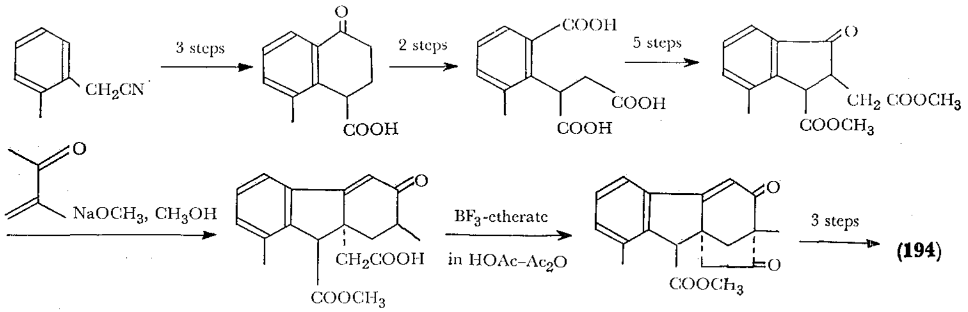
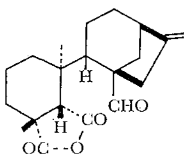

(194)

Loewenthal and Malhotra[92] synthesized (±)-gibberic acid (as **194**), a key degradation product of gibberellic acid from *o*-tolylacetonitrile *via* the route shown in Scheme 3.



Scheme 3

Galt and Hanson[93] converted fujenal (**195**) or 7-hydroxykaurenolide (**196**) to ketotricarboxylic acid mono ester **197** *via* several stpes reactions. The anhydride of compound **197** on pyrolysis at 280° afforded gibbane derivative **198**.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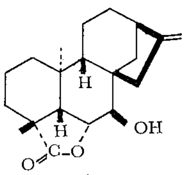
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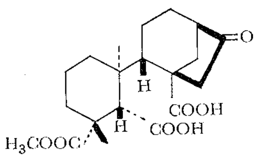
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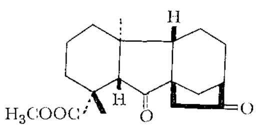
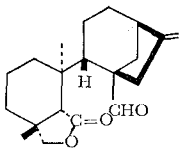

(198)

Fujenal (**195**) on lithium aluminum hydride reduction followed by chromic acid oxidation gave lactone aldehyde **199**, which on base-catalyzed cyclization yielded gibbane derivative **200**. 7-*Epi*hydroxykaurenolide (**201**), a sodium borohydride re-



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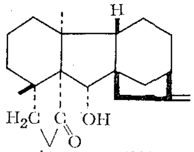
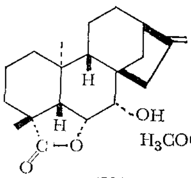
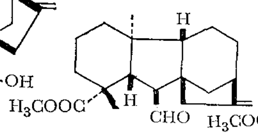


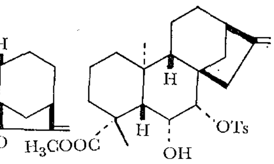
(200)



(201)



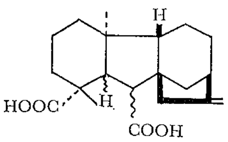
(202)



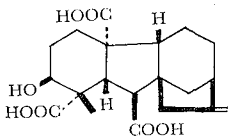
(203)

duction product of 7-oxo-kaurenolide, on tosylation and refluxing with methanolic potassium hydroxide gave, after methylation of the crude product, a 10–15% yield of a B-noraldehyde **202** in addition to a major product **203**.

Cross and Norton[94] isolated a new metabolite gibberellin A_{12} from the culture filtrates of *Gibberella fujikuroi* and showed it to have structure **204**.



(204)



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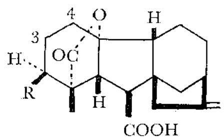
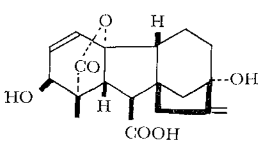


(206): R=OH
(207): R=OH, $\Delta^{3,4}$
(208): R=H

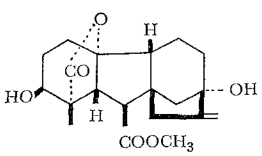
Galt[95] showed the structure of gibberellin A_{13}, a biogenetically interesting new metabolite from *Gibberella fujikuroi*, to be 2β-hydroxy-1β-methylgibbane-1α,4aα,10β-tricarboxylic acid (**205**).

Mulholland *et al.*[96] prepared some new derivatives and transformation products of gibberellic acid. They[97] also reported some reactions with gibberellin A_4 (**206**) and A_7 (**207**).

Hanson and Mulholland[98] described the preparation of 8-demethylene-, 2,3-dehydro-, and some other derivatives of gibberellin A_9 (**208**). Cross *et al.*[99] converted gibberellic acid (**209**) into 7-deoxy compounds. The methyl ester of dihydro-gibberellin A_9 (dihydro-derivative of **208**) was prepared by reduction of ditosylate of gibberellin A_1 methyl ester (**210**) with Raney nickel. A second route utilising the "double inversion" of ring D gave the methyl ester of gibberellin A_4 (**206**).



(209)



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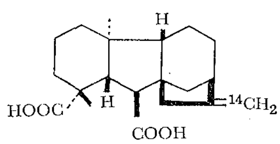

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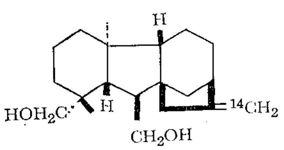

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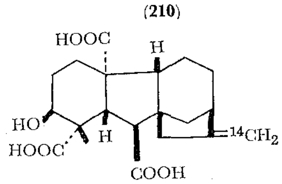


(213)

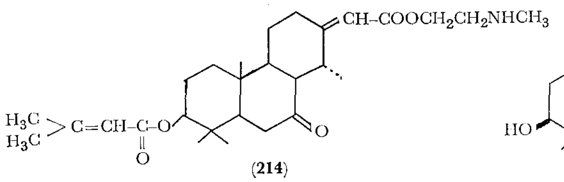
Hanson[100] gave a discussion on the N.M.R. spectra of some gibberellin derivatives in pyridine and deuterochloroform solution. Some differences were correlated with structural features.

Cross and Norton[101] investigated the biosynthesis of gibberellic acid (**209**). They prepared [^{14}C]-gibberellin A_{12} (**211**) and found that the incorporation of **211** into gibberellic acid was disappointingly low (0.7%), but that of the corresponding labelled diol (**212**) which was prepared from **211** by lithium aluminum hydride reduction was high (7.5%). All the radioactivity was shown to be present in the exocyclic methylene group of the gibberellic acid. [^{14}C]-Gibberellin A_{13} (**213**) was isolated from both of the above fermentations. Gibberellin A_{12} and the diol can therefore act as precursors of gibberellic acid, and these compounds together with gibberellin A_{13} may be intermediates, or closely related to intermediates, in the biosynthetic transformation of (−)-kaurene into gibberellic acid.

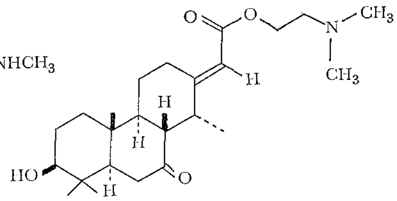
Kucherov *et al.*[102] investigated mass spectrometry of gibberellins and gave dicussions on fragmentations.

VII. DITERPENE ALKALOIDS

Ottinger *et al.*[103] determined the structure of ivorine isolated from the bark of *Erythrophleum ivorensis* as **214**.



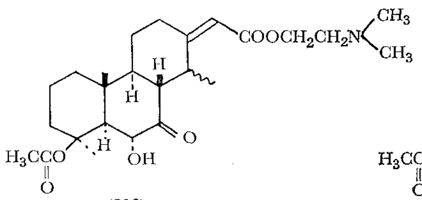
(214)



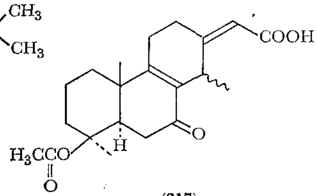
(215)

Hauth *et al.*[104] investigated the absolute configuration of cassaine, an *Erythropheleum* alkaloid, on the basis of N.M.R. analyses. They concluded cassaine to be represented as **215**.

A new alkaloid, erythrophleguine, was isolated from the bark of *Erythrophleum guineense*.[105] The alkaloid proved to have structure **216**. On acid hydrolysis, it gave dimethylaminoethanol and acid **217**.



(216)



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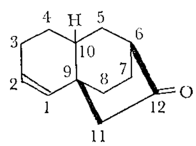


(218)

From Chinese drugs *Hse-Shang-Yi-Zhi-Hao* (*Aconitum bullatifolium var. homotrichum*), aconitine, hypaconitine, bullatine B and three new bases, that is, bullatine E, F, and

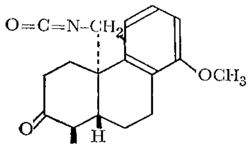
G, were isolated.[106]

Hypaconitine, aconitine, mesaconitine, talatisamine, and two new bases were isolated from Chinese Drugs, *Chuanwu* and *Fu-tsu* (*Aconitum carmicaeli*).[107]

Singh and Singh[108] isolated five diterpene alkaloids, that is, vakognavine, an ether-soluble alkaloid which appeared to be palmatisine, vakatisine, and vakatidine, from the roots of *Aconitum palmatum*.

Finnegan and Bachman[109] synthesized ($\pm$)-12-oxo-6,9-ethano-*cis*-$\Delta^{1,2}$-octalin (as **218**), a potentially useful intermediate for the total synthesis of atisine.

Wiesner *et al.*[110] treated isocyanate **219** with *p*-toluenesulfonic acid in refluxing benzene for 32 hours and got a keto lactam **220** in 26% yield. The lactam on two steps of reductions gave amine **221**.



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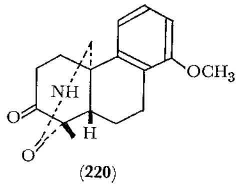

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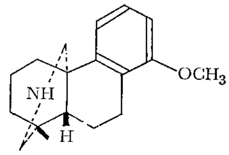
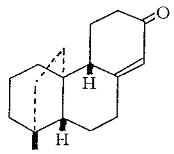


(221)

They also tried a photochemical approach to the C-D ring system of atisine; irradiation of a 1% solution of enone **222** in dry tetrahydrofuran in the presence of a large excess of allene at –80° for 13 hours resulted in a complete conversion to compound **223**. The latter was converted to compounds **224** and **225** *via* several steps.



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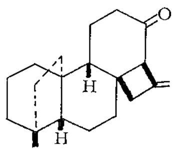

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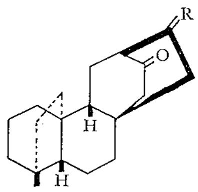
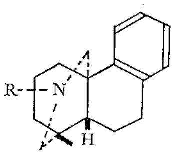
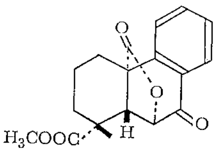


(224): R=$\langle$OH, H
(225): R=O

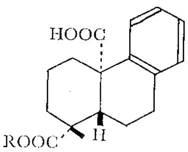
Tahara *et al.*[111] carried out syntheses of optical active compounds **226** and **227** from abietic acid (**4**). As the total synthesis of abietic acid has been accomplished,[112] the syntheses of **226** and **227** from abietic acid can be regarded as formal total syntheses of these compounds.



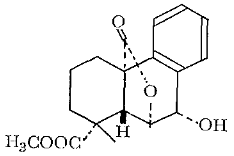
(226): R=H
(227): R=Ac



(228)



(229): R=CH_3
(231): R=H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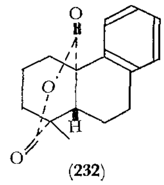
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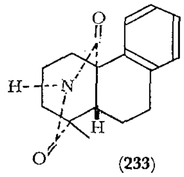
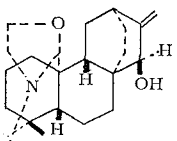
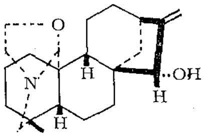

(233)

They derived, as a key intermediate, keto lactone ester **228** from abietic acid. Subsequent hydrogenolysis of the compound on 30% palladium-charcoal in acetic acid containing a small amount of sulfuric acid at 35–40° gave an acid **229** and a lactone alcohol **230**. Alkaline hydrolysis of the acid afforded dicarboxylic acid **231**, which was dehydrated by heating with acetic anhydride to give an anhydride **232**. Treatment of the latter with urea gave imide **233**, which on lithium aluminum hydride reduction yielded compound **226**.

Pelletier and Locke[113] reported the details of the correlation of atisine (**234**) and veatchine (**235**) *via* the bisnor ester **236**. Atisine was converted to dicarboxylic acid derivative **237** and then selective decarboxylation was achieved *via* Hunsdiecker reaction of **238** followed by removing the bromine in product **239** with zinc in glacial acetic acid containing a few drops of hydrochloric acid.


(234)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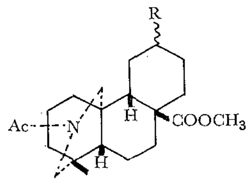
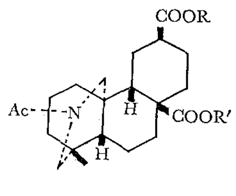
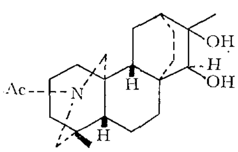
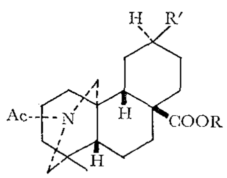
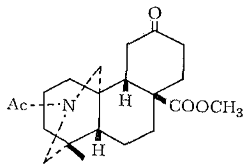

(236): R=H
(239): R=Br


(237): R=H, R′=H
(238): R=Ag, R′=CH_3

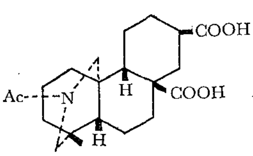
Another route was also successful; the key intermediate **240** derived from atisine on oxidation with Kiliani reagent gave a seco acid **241**. Subsequent Baeyer-Villiger reaction and saponification gave hydroxy acid **242**, the methyl ester (**243**) of which on chromic acid oxidation gave keto ester **244**. The latter was converted to the thioketal and reduced with Raney nickel to give the desired bisnor ester **236**. Thus, atisine has been converted to the bisnor ester **236** by two independent routes.


(240)


(241): R=H, R′=Ac
(242): R=H, R′=OH
(243): R=CH_3, R′=OH


(244)

Conversion of veatchine to the bisnor ester **236** was successful by a sequence of reactions paralleling the first route described for conversion of atisine to **236**; veatchine was converted to bromo derivative **246** *via* dicarboxylic acid **245** and then to **236**. This correlation provides the first unequivocal evidence for the common stereochemistry of the atisine- and *Garrya*- type alkaloids.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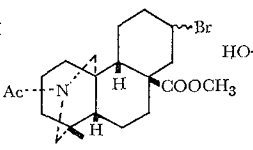
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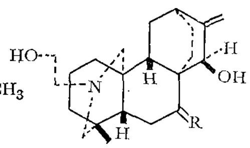
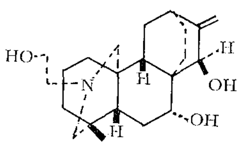
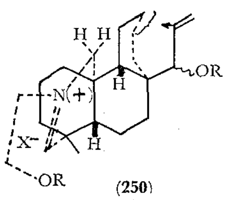

(247): R=O
(248): R=H_2

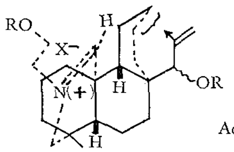

(249)

Pelletier and Parthasarathy[114] published the details of their work on atisine chemistry and gave discussions to certain interesting chemical features of the atisine molecule.

Pelletier[115] published a paper which details the elucidation of the structure (**247**) of atidine isolated from *Aconitum heterophyllum* and its correlation with the *Delphinium* alkaloid, ajaconine; Huang-Minlon reduction of atidine (**247**) furnished dihydro-atisine (**248**). Reduction of atidine with sodium borohydride afforded a mixture, one of the components of which was identical with dihydroajaconine (**249**). Thus the keto function was assigned to position 7 in atidine.

Pelletier *et al.*[116] studied the isomerization of iso-type diterpene alkaloid salts to normal-type salts. The iso-type diterpene salts (**250**) were smoothly isomerized to the normal-type salts (**251**) at reflux temperature in such polar solvents as N, N-dimethyl-acetamide, N, N-dimethylformamide, dimethyl sulfoxide, phenol, the cellosolves, and carbitols. The isomerization follows first-order kinetics and the rate is greater in the proton-donor type solvents than in the non-donor type. The effect of temperature on the rate of isomerization of isoatisinium chloride in several solvents was investigated. The energy of activation, enthalpy of activation, entropy of activation, and frequency factor were calculated for isomerization in various solvents.


(250)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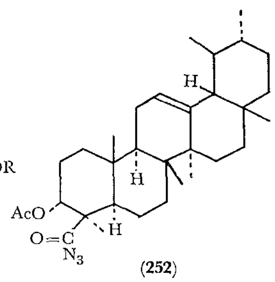
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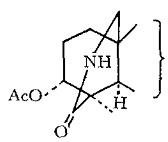
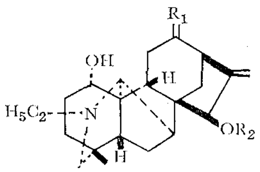

(253)

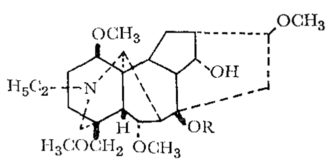
Huneck[117] investigated a photochemical cyclization of 3α-acetoxy-urs-12-ene-24-carboxylic acid azide (**252**) to lactam **253**.

Okamoto *et al.*[118] reported the result of the crystallographic study of lucidusculine hydriodide; the structure of lucidusculine (**254**), an alkaloid of the roots of *Aconitum lucidusculum*, was settled on firm basis as a diterpene alkaloid possessing the (—)-kaurene carbon skeleton. The structure of songorine, an aconite alkaloid, had been determined, but for the purpose of establishment of its absolute configuration, songorine was reduced with lithium aluminum hydride to furnish a crystalline product. It was identified with luciculine (**255**), an alkamine of lucidusculine, hence the structure of songorine was confirmed to be **256**.

Canadian school and Japanese school[119] presented a structural formula **257** to chasmanine, an alkaloid from *Aconitum chasmanthum*.



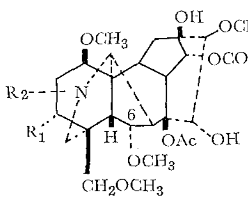
(**254**): R_1= ·OH, H, R_2=COCH$_3$
(**255**): R_1= ·OH, H, R_2=H
(**256**): R_1=O, R_2=H



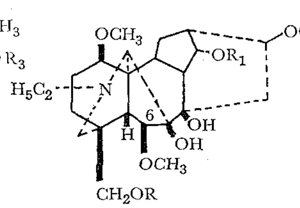
(**257**): R=H
(**258**): R=CH$_3$

Achmatowicz, Jr. and Marion[120] suggested structure **258** for homochasmanine isolated from *A. chasmanthum*.

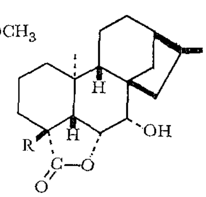
Marion *et al.*[121] found a remarkable difference in the oxidations of two groups of diterpene alkaloids; group A (as **259**), to which aconitine-like bases possessing α-configurational C–6 methoxyl group belong, on oxidation with permanganate at room temperature in the neutral medium afforded dealkylated secondary bases, whereas group B (as **260**), to which lycoctonine-like bases possessing β-configurational C–6 methoxyl group belong, on same treatment furnished the corresponding lactams. Thus, the characteristic difference can be used for assignment of the stereochemistry at C–6 of these alkaloids.



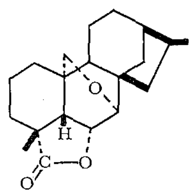
(**259**)



(**260**)

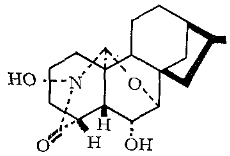


(**261**): R=CH$_3$; dihydro derivative of 201
(**263**): R=H
(**264**): R=CH$_2$OH

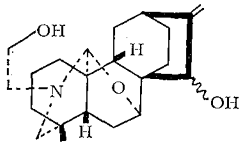


(**262**)

Barton and Hanson[122] irradiated 7α-alcohol **261** derived from 7-hydroxykaurenolide (**196**), in benzene solution in the presence of iodine and lead tetraacetate, and got an ether **262** in high yield. They also carried out photolysis of the nitrite of the 7α-alcohol **263** derived from 7,18-dihydroxykaurenolide (**264**) and obtained a lactam **265**. The reaction clearly has potential for the partial synthesis of ajaconine (**266**).

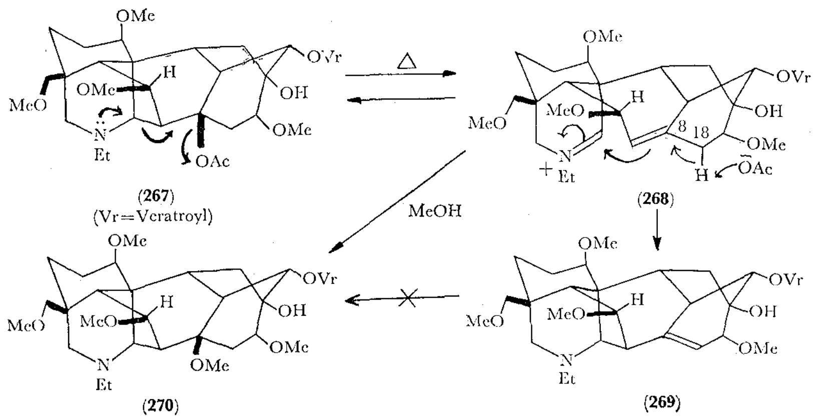


(265)



(266)

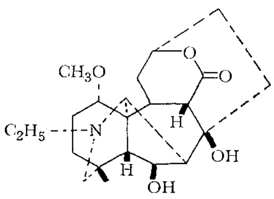
The mild pyrolytic loss of acetic acid from diterpene alkaloids of aconitine type **267** (bikhaconitine) and the formation of the "pyro"-compound **269** was examined and evidence that such reactive intermediates as **268** exist has now been provided by Edwards.[123] This reaction is interpreted as rapid reversible formation of ionic species **268**, followed by a slower attack of acetate ion on the 18-hydrogen, as shown in Scheme 4. The replacement of the acetoxy-group by a methoxy-group at 130° is similarly explained as attack of methanol on C-8 of **268**, with re-establishment of the original skeleton (**268**→**270**).



Scheme 4

The structure and relative stereochemistry of the lactone-type diterpene alkaloid heteratisine (*Aconitum heterophyllum*) had been established by crystallographic and chemical methods. The absolute configuration **271** had been suggested on the basis of the expected biogenetic relationship to the aconitines possessing the regular lycoctonine-type skeleton. Aneja and Pelletier[124] presented further evidence and arguments which establish the absolute configuration of heteratisine as **271** from a study of the optical rotatory dispersion curve of pyroheteratisine, (and its derivatives) a product obtained from esters of heteratisine by way of a facile thermally-induced ring cleavage reaction.

Wiesner *et al.*[125] synthesized a compound **273** from methoxy tetralone **272** *via* a number of steps.



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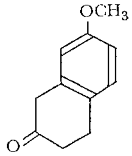
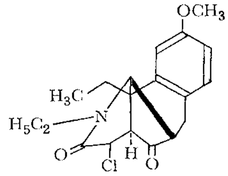


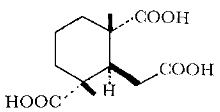
(272)



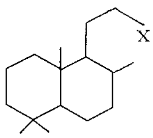
(273)

VIII. THE OTHERS

Raphael *et al.*[126] carried out a stereoselective synthesis of meso-*trans*-1, 3-dimethyl-cyclohexane-2-acetic-1,3-dicarboxylic acid **274** which is a key compound for the determination of the stereochemistry of ring A through drastic oxidation of diterpenoid resin acids.



(274)



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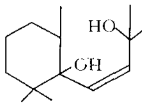

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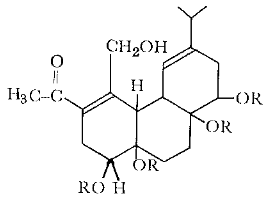
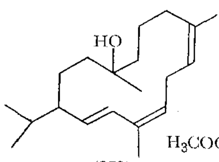
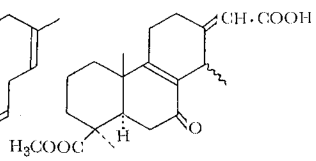


(277)

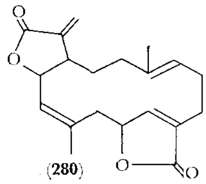
Blake and Jones[127] tried an approach to elaborate decalins of type **275** from 2,2,6-trimethylcyclohexanone through an acetylenic intermediate. But they got only compound **276**. Arroyo and Holcomb[128] published the isolation of a pure crystalline active tumour-enhancing compound from *Croton* oil and presentation of partial structure **277** to the substance. Lisina *et al.*[129] isolated abietinal and two new diterpenes, together with some sesquiterpenoids, from high boiling portion of cedar resin. One of the new diterpenes, cembrol was shown to have structure **278**. Another one was shown to be a diterpene diol.



(278)



(279)



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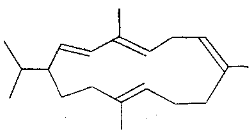
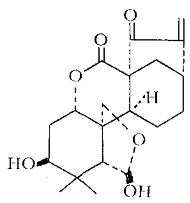


(281)

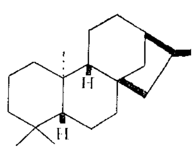
Chapman *et al.*[130] elucidated the structure of dehydrocassamic acid which was isolated from the bark of *Erythrophleum guineense* as shown in formula **279**. Immer *et al.*[131] presented structure **280** to ovatodiolide, a macrocyclic diterpene from *Anisomeles ovata*.

Dauben *et al.*[132] published a detailed report on the structure elucidation, by systematic degradation, of cembrene (**281**), a monocyclic diterpene hydrocarbon from the oleoresin of many pine trees of the subgenus *Haploxylon*. The work had been reported as a preliminary communication.[133]

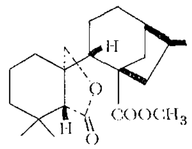
Transformation of enmein, a bitter principle of *Isodon trichocarpus*, into (−)-kaurane (**283**) was independently accomplished by two Japanese groups, and the absolute configuration of enmein (**282**) was confirmed by the chemical evidence; Okamoto *et al.*[134] derived the key intermediate **284** from enmein *via* hydroxylactone ester **285** and unsaturated ester **286**, whereas Fujita *et al.*[135] derived the same key compound (**284**) *via* 15-deoxo-dehydrodihydroenmein (**287**) or its acetate (**288**). The acyloin condensation of **284** was carried out with sodium in boiling toluene by Okamoto's group, while the same reaction was done with sodium in liquid ammonia by Fujita's group. The main product **289** was converted to (−)-kaurane (**283**) by a common route.



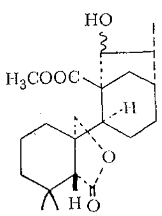
(**282**)



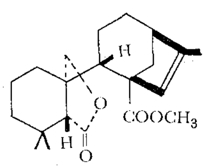
(**283**)



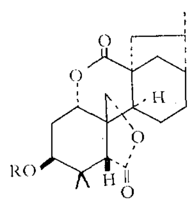
(**284**)



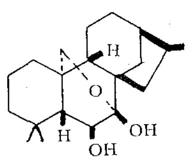
(**285**)



(**286**)

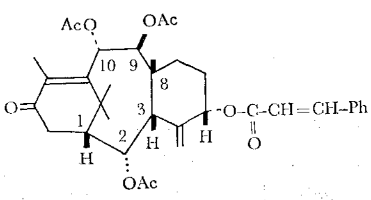


(**287**): R=H
(**288**): R=Ac

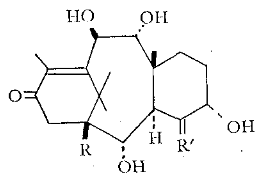


(**289**)

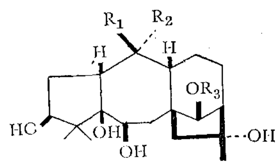
Nakanishi, Uyeo *et al.*[136] presented a stereochemical structure **290** to taxinine (=0-cinnamoyltaxicin-II triacetate). Against this, Lythgoe *et al.*[137] published an evidence that a complete stereochemistry of 4, 16-dihydrotaxicin-I corresponds to structure **291**, thus taxicin-II should be represented as structure **292**.*



(**290**)



(**291**): R=OH, R′= $<^{CH_3}_{H}$
(**292**): R=H, R′=CH_2



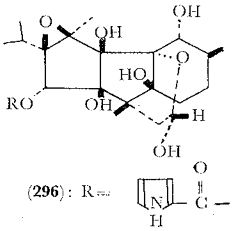
(**293**): R_1=CH_3, R_2=OH, R_3=Ac
(**294**): R_1R_2=CH_2, R_3=H
(**295**): R_1=CH_3, R_2=OH, R_3=H

* Recent X-ray analysis by Nakanishi, Uyeo *et al.* resulted in a complete agreement with Lythgoe's conclusion. (*Chem. Comm.* **1966,** 97)

Uyeo *et al.*[138] published in detail a previous data for partial elucidation of the structure of taxinine.

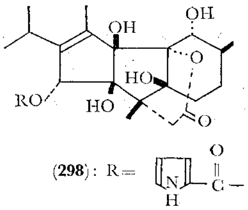
Nakanishi *et al.*[139] published a full paper of stereochemistry of grayanotoxins. Grayanotoxin-I, -II, and -III, the toxic components of *Leucothoe grayana* are shown as **293**, **294** and **295**, respectively.

Wiesner *et al.*[140] presented a complete structure of an insecticide ryanodine, a constituent of *Ryania speciosa*; ryanodine, ryanodol, anhydroryanodine, and anhydroryanodol can be represented as **296**, **297**, **298** and **299**, respectively.



(**296**): R=

(**297**): R=H



(**298**): R=

(**299**): R=H

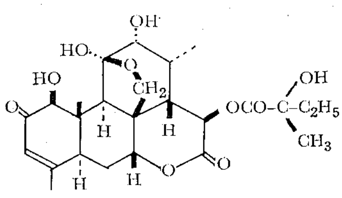
Narayanan and Venkatasubramanian[141] investigated the signals of C–4 and C–10 methyls in the N.M.R. spectra of many kinds of diterpene acids and their esters.

Weiss *et al.*[142] published a review on ORD or CD studies of a great number of non-polar homoannular cisoid dienes. Levopimaric acid (**1**) and palustric acid (**2**) were discussed in the review.

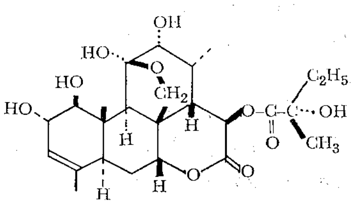
Enzell and Ryhage[143] recorded the mass spectra of 45 dicyclic diterpenes (labdane group) and interpreted them. The spectra of Δ^{7}-unsaturated diterpenes, $\Delta^{8(20)}$-unsaturated compounds, compounds with a C–8 OH group, and the terpenes with C–8–C–13 ether bridge were discussed.

Clayton[144] described biosynthesis of diterpenoids in a short section in his review of biosynthesis.

Finally, quassin-analogous compounds will be described. Gaudemer and Polonsky[145] presented structure **300** to glaucarubinone isolated from *Simaruba glauca*. Yates *et al.*[146] discussed the absolute configuration of glaucarubin and pointed out incorrect relative configuration of the side chain. They presented a correct configuration **301** of glaucarubin.

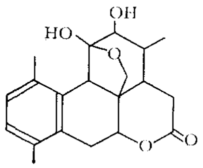


(**300**)

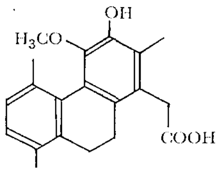


(**301**)

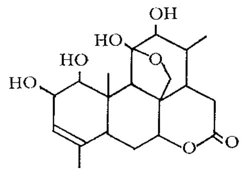
de Mayo *et al.*[147] published that chaparrin, a bitter principle of *Castela nicholsonii*, on two steps degradations gave a partially aromatized product, chaparrol (**302**), which was converted, by stepwise degradations, into dihydrophenanthrene derivative **303**. Thus, chaparrin was shown to have structure **304**.



(**302**)

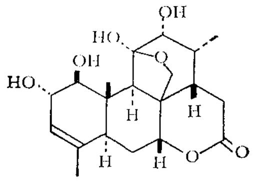


(**303**)

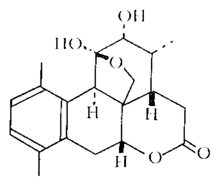


(**304**)

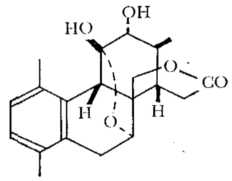
Subsequently, de Mayo *et al.*[148] investigated the stereochemistry of chaparrin and related compounds. They presented the absolute configurations **305**, **306**, **307** and **308** to chaparrin, chaparrol, isochaparrol, and neochaparrol, respectively.



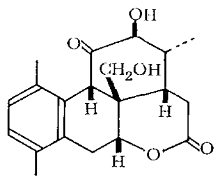
(**305**)



(**306**)

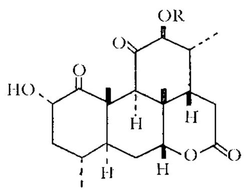


(**307**)

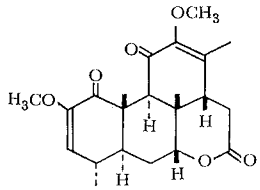


(**308**)

Casinovi *et al.*[149] isolated amarolide and its monoacetate, and presented structural formulas **309** and **310**, respectively, on the basis of correlation with quassin (**311**).



(**309**): R=H
(**310**): R=Ac

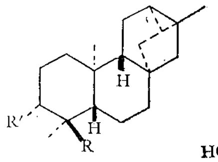


(**311**)

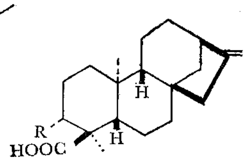
SUPPLEMENT

Moody[150] tried a preliminary work on the synthesis of marrubiin. The wood resin of *Agathis australis* was investigated by Enzell and Thomas.[151] Lin and Liu[152] extracted shonanol, a new diterpene phenol, from the wood of *Libocedrus formosana*.

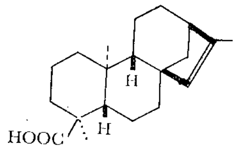
Ourisson *et al.*[153] isolated novel diterpenes related to labdane, kaurane, and a new parent hydrocarbon **312**, which was named trachylobane, from deseeded pods of *Trachylobium verrucosum*; trachylobanol (**313**), trachylobanic acid (**314**), kaurenoic acid (**315**), isokaurenoic acid (**316**), 3-acetoxy-trachylobanic acid (**317**), 3-acetoxy-kaurenoic acid (**318**), and zanzibaric acid. The structures of the new diterpenes were determined by spectral data and chemical degradations; a correlation between derivatives of kaurane and trachylobane was shown.[154] Reactions of trachylobane derivatives were investigated.[155] Finally, the structure of **319**, a new compound extracted from *T. verrucosum* as acetate and named zanzibaric acid, was determined by degradation and from spectral data.[156]



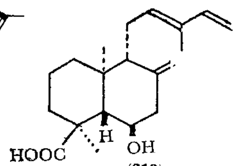
(**312**): R=CH_3; R′=H
(**313**): R=CH_2OH; R′=H
(**314**): R=COOH; R′=H
(**317**): R=COOH; R′=OAc



(**315**): R=H
(**318**): R=OAc



(**316**)



(**319**)

The isolation of levopimaric acid from pine oleoresin has been described in Organic Syntheses.[157] A report of discussion on absolute configuration at C-13 of labdanolic acid has been published.[158] A review of recent studies on diterpene alkaloids by an Italian author has been published.[159]

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